REMARKS

i. Status of the claims and application

Claims 1, 5-13, and 56-62 are pending. Claim 1 has been amended.

Applicant thanks Examiner Pryor for extending the courtesy of several telephone interviews in July and August of 2004, with the undersigned, including discussions pertaining to present claim 1. Based on those discussions, Applicant amended claim 1 to recite a "composition useful for treating a hematological cancer in a mammal, consisting essentially of (A) at least one arsenic sulfide compound, and (B) a pharmaceutically acceptable carrier or excipient."

Applicant also amended claim 1 to recite a composition that "consists essentially of" an "arsenic sulfide compound" and deleted the objectionable phrase "substantially free of arsenic impurities." Applicant discussed this phrasing with Examiner Pryor and agree with him that the transition "consists essentially of" excludes the presence of arsenic trioxide in the arsenic sulfide compound.

For this reason, and as the Examiner acknowledged via telephone conference with the undersigned, Yang *et al.*, CN 1061908, does not anticipate claims 1-5 and 14 because Yang's composition is a pulverized mixture of, among other ingredients, unpurified realgar ore and arsenic trioxide. Hence, Applicant requests that the rejection in light of Yang be withdrawn.

ii. The present claims are not anticipated by Ellison because Ellison does not teach an arsenic sulfide compound for treating a hematological cancer that excludes arsenic trioxide

The Examiner maintained his rejection of claims 1, 5-8, 11-13, 61, and 62 under 35 U.S.C. § 102(e) as allegedly anticipated by Ellison *et al.*, USSN 2002/0183385. The Examiner characterizes Ellison as "a composition comprising one or more arsenic compounds ... in a carrier ... to be used in cancer treatment of mammals" (Office Action at page 3).

Yet Ellison is concerned with "treating solid tumors," *i.e.*, with treatment of cancers of a body tissue. There would have been no basis *a priori* for generalizing from such cancer treatment to dealing with a cancer of the blood, bone marrow, or lymphatic system, *i.e.*, a

"hematological cancer," as recited. Ellison himself recognizes this distinction, noting that "there are a plethora of different types of cancers, each of which requires a unique treatment protocol" (page 3, paragraph 24).

To this end, Ellison concluded that arsenic *trioxide* can be used to treat a broad range of cancers, specifically, "non-small cell lung cancer, colon cancer, central nervous system cancer, melanoma, ovarian cancer, renal cancer, prostate cancer, and breast cancer" (page 12, paragraph 102), but concludes nothing about the treatment of a hematological cancer with arsenic *sulfide*. Furthermore, in contrast to claim 1 of the present invention, Ellison does not contemplate the use of an arsenic sulfide compound that is *substantially free of arsenic impurities*, such as arsenic trioxide. To the contrary, Ellison's anti-cancer agent specifically comprises arsenic trioxide. Thus, for at least these reasons, Ellison does not anticipate the present claims and Applicant, therefore, respectfully requests that the Examiner withdraw this rejection.

iii. Claims 56 and 57 are not rendered obvious by Ellison because the prior art (a) did not identify arsenic sulfide as an anti-cancer agent, and (b) would have deemed it non-sensical to reduce the amount of arsenic trioxide in a pharmaceutial because arsenic trioxide was known to be an effective anti-cancer agent

The Examiner rejected claims 56 and 57 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ellison, *supra*. According to the Examiner, Ellison "teaches all that is recited in claims 56 [and] 57, except for the composition comprising the instant amount of arsenic sulfide. It would have been obvious ... to determine the optimum amount of arsenic sulfide" (Office Action at page 3). The Examiner asserts that "[O]ne would have been motivated to do this in order to develop a composition that would have been most effective in treating cancer" (Office Action at page 3).

Claims 56 and 57 qualify the pharmaceutical composition of claim 1 as containing less than 0.15% and less than 0.1% of arsenic trioxide, respectively. Contrary to the Examiner's reasoning, the skilled artisan would not have been motivated to *reduce* the amount arsenic trioxide to such levels, because the skilled artisan would have known that arsenic trioxide was a well-documented, anti-cancer agent. Thus, it would have been paradoxical for the skilled artisan to reduce, in a pharmaceutical composition, the quantity of a substance that was known to be effective in treating cancer. Accordingly, he would not

have been motivated to reduce the amount of arsenic trioxide to make Ellison's arsenic sulfide composition "substantially free of arsenic impurities."

Corroborating this lack of motivation is the skilled artisan's understanding that arsenic sulfide was a harmful, if not poisonous, substance. The skilled artisan would have been aware that since the early 1970s, only arsenic trioxide had been considered a suitable anticancer agent (Zhu *et al.*, Nature Reviews Cancer 2(9): 705-13, 2002). Accordingly, the perceived toxicity (see following subsection) and intermediate nature of arsenic ores, *i.e.*, their use as combustible intermediates for producing As_2O_3, likely led away from their use as anticancer medicaments alone.

Before April 24, 1998, which is the effective filing date of the present application, there was nothing in the art to suggest purifying arsenic sulfide from a natural ore and then administering it to treat cancer, with or without an additional, therapeutic excipient. In 1985, for example, Pershagen & Bjorklund, Cancer Lett. 27(1): 99-104 (1985), found that calcium arsenate "is tumorigenic" and that "the evidence is inconclusive for arsenic trisulfide" (abstract previously submitted). Similarly, a "human carcinogenicity of arsenic" study reported by Tinwell *et al.*, Environ. Health Perspect. 95: 205-10 (1991) (abstract appended), prompted the conclusion that "the natural ore orpiment (principally As_2S_3) was *inactive* despite blood level of arsenic of 300 to 900 ng/mL in treated mice" (emphasis added). Li *et al.*, Zhongguo Zhong Yao Za Zhi 22: 327-9 (1997) (abstract previously submitted), characterized realgar and its sublimates as "poisonous" drugs.

Substantiating this understanding is a recent publication co-authored by the inventor. Thus, Lu *et al.*, Blood 99(9): 3136-43 (2002), reiterated that "realgar as mined" can produce a variety of "toxic effects," especially since different preparations of ore probably would result in different purities of As_4S_4 content. See "Discussion" at page 3142, and page 7 of the present specification, at lines 16-25.

In fact, Dr. Lu notes that although realgar was in common use heretofore, it was actually "employed with several herbal drugs containing hundreds of components." In other words, many putative active ingredients existed in any one preparation. It would not have been possible, therefore, to discern a medicinal affect specifically attributable to realgar, let

alone to arsenic sulfide. Since medical efficacy had been attributable to the combination of various amounts of various different active ingredients, therefore, it would not have been possible for the skilled artisan to determine *any* amount of an arsenic sulfide compound, substantially free of arsenic impurities, that was effective in treating hematological cancer. Furthermore, as discussed above, he would have had no motivation to *remove* arsenic trioxide from the arsenic sulfide compound.

Finally, Ellison taught that each cancer requires "a unique treatment protocol" (page 3, paragraph 24), so the skilled artisan would have understood that not all cancer treatment strategies are fungible. Therefore, contrary to the Examiner's assertion, Applicant believes that before the present invention, no arsenic sulfide compound, substantially free of arsenic impurities had ever been categorized as effective against any hematological cancer when used in isolation from its natural ore. For at least these reasons, Applicant asserts that claims 56 and 57 are not rendered obvious by Ellison and respectfully request that the Examiner withdraw this rejection.

v. Conclusion

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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